REMARKS

Claims 1 and 2 are under examination. Claims 1-9 are pending and claims 3-9 have been withdrawn. New claims 10-33 are added.

Claims 1 and 2 have been amended to add the term "*in vitro*." Support for the amendment is provided throughout the specification, e.g., at page 12, lines 13-30.

The specification has been amended on page 7 to conform to the Office's requested change to the labeling of Fig. 11. In addition, a substitute abstract is provided on a separate sheet.

Support for the new claims in provided throughout the specification. For example, support for claims 10, 12, 13, and 15-17 is found at page 3, lines 4-8; claim 11 at page 18, line 16; claim 14 at page 6, lines 5-7; claim 18 at page 13, line 27; claim 19 at page 18, lines 11-24; claims 20-22 at page 25, lines 11-15; claims 23-25 at page 13, line 5 and page 14, lines 7-19; claims 26-31 at page 9, line 14-page 12, line 14, and page 33, lines 14-20; and claims 32-33 at page 15, line 25-page 17, line 22 and page 33, lines 14-20.

No new matter is added by the amendments.

Drawings

The drawings were objected to because Fig. 11 contained two parts, an upper panel and lower panel. In compliance with the Office Action, Fig. 11 has been redrawn to label the upper and lower panels "Fig. 11A" and "Fig. 11B," respectively. The specification has been amended to reflect the changes in Fig. 11.

Specification

The Office Action indicates that the disclosure does not contain an abstract as required by 37 CFR 1.72(b). A new abstract has been provided on a separate sheet. The new abstract is identical to the original abstract except that the title of the application that was on the abstract page has been deleted.

35 U.S.C. § 112, first paragraph, enablement

Claims 1 and 2 have been rejected for lack of enablement because while the disclosure has been deemed to be enabling for a method of identifying a compound that stabilizes or can stabilize an α-helical conformation of a discordant helix in a polypeptide *in vitro*, the Office Action states that the specification is not enabling for practice of the method *in vivo*. To expedite prosecution, the claims have been amended to indicate that method is carried out *in vitro*.

In view of the amendment to the claims, Applicant requests that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

35 U.S.C. § 102

Claims 1 and 2 have been rejected for anticipation by Soto et al. (1996, Biochem. Biophys. Res. Comm. 226(3):672-680) and Salomon et al. (1996, Biochem. 35:13568-13578). Applicant respectfully disagrees with the rejection.

To anticipate a claim, the reference must teach every element of the claim. The claims are drawn to a method of identifying a compound that stabilizes an α-helical conformation of a discordant helix in a polypeptide. The method includes providing a test sample polypeptide that contains a discordant helix in the form of an α-helix, contacting the sample with a test compound, and determining the rate of decrease in the amount of α-helix in the test sample (claim 1) or determining the amount of α-helix (claim 2). Applicant submits that neither Soto et al. nor Salomon et al. teaches every element of the claims.

Soto et al. and Salomon et al. are discussed separately below. First, however, Applicant wishes to clear up an apparent misunderstanding that seems to underlie the rejections over both of these references. The Examiner appears to believe that measuring amyloid is the same as measuring α-helix, and furthermore that α-helix is the same as random coil. Neither assumption is correct. An individual molecule of a polypeptide such as Aβ can exist partly or wholly in the form of α-helix (a particular type of ordered structure), soluble β-sheet (another type of ordered structure), or random coil (a structure having less order than α-helix and β-sheet); or it can be in the form of precipitated β-sheet, also termed "amyloid." Since a molecule can exist in any of

these forms, measuring the amount of any one of those forms present in a sample is not directly or indirectly equivalent to measuring any other.

Soto et al.

As outlined above, claim 1 requires the step of determining the rate of decrease in the amount of α-helix in the test sample, while claim 2 requires determining the amount of α-helix in the sample. Soto et al. makes no reference whatsoever to determining the rate of decrease or the amount of α-helix in a sample. The most nearly analogous technique taught by Soto et al. is the use of a fluorescence spectrometer to detect fluorescence emission of thioflavine T as a measure of amyloid formation and preformed fibril disaggregation (page 673, Materials and Methods). According to Soto et al., thioflavine T binds to amyloid and permits quantification of the amount of amyloid in the sample. Soto et al.'s technique therefore measured amyloid, not α-helix as required by the claims. As established above, the two are not equivalent. Thus, Soto et al. cannot anticipate the claims.

As a second and independent ground for withdrawal of the rejection, Applicants note that Soto et al. does not teach the claim limitation of providing a test sample comprising a polypeptide that contains a discordant helix in the form of an α-helix. A discordant helix is defined in the specification as "[a]n amino acid sequence that is present as a helix in a polypeptide but is predicted to form a β-strand structure" (specification at page 2, lines 17-18). The claims specifically require the discordant helix in the sample to be in the form of an α-helix. The Office Action relies on the fact that Soto et al. focused on the tendency of a portion of the Aβ protein (residues 15-25) to form β-strand, apparently in an attempt to show that the Aβ protein meets the "predicted to form a β-strand structure" part of the definition. The other part of the definition of "discordant helix" (that the sequence be in the form of a helix), and the further requirement explicit in the claims that the sequence be in the form of an α-helix, are ignored by the Office Action. In fact, nothing in Soto et al. suggests that the test sample actually included a polypeptide containing a sequence present as a helix, nor that the helix is an α-helix. Soto et al. simply didn't address it.

In view of the foregoing, Applicant believes that Soto et al. does not anticipate the pending claims and respectfully requests that the rejection be withdrawn.

Salomon et al.

The Office Action says, "Salomon et al. clearly suggests performing a screening method to identify substances that prevent β-sheet formation..." (Office Action at page 7, item 18). While a substance that prevents β-sheet formation might also give a positive readout in the claimed methods, that certainly does not mean that Salomon et al.'s screening method anticipates the claims. As described previously, the claims are drawn to methods that include the step of determining the rate of decrease or the amount of α-helix in a sample that contains discordant helix in the form of α-helix. Salomon et al. does not disclose such a method. The three assays described in Salomon et al. are summarized below.

Both the first assay (utilizing circular dichroism (CD)) and the second assay (utilizing ultraviolet spectroscopy) began with preparations of Aβ polypeptide pretreated by sonication in TFA, which the authors state produces "monomeric random coil structures" (page 13569, col.1). There is no suggestion that these preparations also contained, in addition to the random coil structures, α-helix. Much less is there any hint that some portion of the Aβ polypeptide that might be predicted to take both α-helical and β-strand forms as characteristic of the "discordant helix" (defined in the present application) was in the α-helix form in either of these first two assays. Thus, the first and second assays fail to meet that limitation of the claims.

Furthermore, the first analytical method described by Salomon et al. utilized CD to study changes in secondary structure over time. As explained by Salomon et al. on page 13569, col. 1-2, this technique was used to measure the amount of soluble β-sheet structure in the sample. Salomon et al. report that in the absence of nicotine (an inhibitor of aggregation), the Aβ solution used in the experiment is a mixture of only two conformations, β-sheet and random coil (page 13571, col. 1). The results of CD measurements in the presence of nicotine suggest that more than two conformations exist (page 13571, col.1), but Salomon et al. does not speculate

what they may be. Regardless of whether α-helix is present, clearly Salomon et al. did not measure α-helix, so this method is not within the present claims.

The second analytical method described by Salomon et al. is a precipitation assay using ultraviolet spectroscopy to measure the amount of polypeptide remaining in the supernatant after removal of insoluble aggregates using centrifugation (see page 13569, col. 2; and page 13571, col. 2). This technique measures total polypeptide remaining in the supernatant, which could be in any soluble form, including α-helix, soluble β-sheet, random coil, or mixtures. It certainly is not a method of determining the amount of α-helix, or the rate of decrease of α-helix, in the sample. Thus, the second technique described by Salomon et al. is not covered by the present claims.

The third analytical method described by Salomon et al. utilized nuclear magnetic resonance (NMR) to detect binding of nicotine to specific residues of an Aβ peptide. While these NMR experiments did utilize the Aβ polypeptide in α-helical form (page 13572, col. 1-2), neither the amount of α-helix nor the rate of decrease of α-helix was determined. Rather, Salomon et al. used this technique merely to identify which residues of the Aβ polypeptide were bound by nicotine. Thus, the third technique described by Salomon et al. is not within the present claims.

For at least the reasons presented in the arguments presented above, Applicant believes that neither Soto et al. nor Salomon et al. anticipates the pending claims, and respectfully requests that the rejections under 35 U.S.C. § 102 (b) be withdrawn.

CONCLUSION

Applicant believes that the claims are in order for allowance, which action is requested. Please apply any charges or credits to deposit account 06-1050, referencing attorney docket number 12125-002001.

Respectfully submitted,

Date: September 2, 2003

Lisa N. Geller, Ph.D., J.D.
Reg. No. 51,726

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906